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R.L. SPHAR, CAPT, MC, USN
Commanding Officer
Naval Medical Research Institute

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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Evaluation and Treatment of Nuclear Casualties: Part I — Acute Radiation Syndrome and Triage

Lt Col James J. Conklin, MD, MC, USAF*

Lt Dennis L. Kelleher, MSC, USANR**°

CDR Richard Walker, MSC, USN'

A current review on the treatment of nuclear casualties and some of the possible new immunological techniques and other therapeutic interventions that may be useful in the medical arsenal will be presented in the Medical Bulletin in three parts in the next three issues of the journal.

Introduction

The medical officer in support of the operational commander carries the dual responsibility to provide medical care for combat casualties and to advise the commander on the operational capabilities of his troops. With conventional combat injury the mission, while demanding, is accomplished according to relatively established triage and patient care procedures. In the case of the nuclear battlefield, however, we are less certain of the adequacy of current triage and patient care procedures. Also on the nuclear battlefield the medical officer will be asked to judge the operational capabilities of troops that are free of signs or symptoms yet have suffered potentially lethal injury, a scenario quite unlike conventional warfare. Any lack of operational readiness of medical support units to function in a nuclear environment is due largely to three factors. First and foremost there is admittedly a reluctance on the part of all people including military medical personnel to contemplate nuclear warfare, much less medical operations on the nuclear battlefield. By exten-

sion, the enormity of nuclear war has clouded the whole issue of medical preparedness in a "nuclear environment." By "nuclear environment" we mean the world we live in today; a world of nuclear energy, nuclear waste, accidental radiation exposure, and the increasing possibility of nuclear terrorism. Furthermore, radiobiologic research has not kept pace with this expanding nuclear environment. Development of innovative diagnostic and therapeutic regimens for radiation injury has slowed in recent years due to a perceived lack of requirement. Thus, we are left with concepts of radiation injury and treatment essentially unchanged since the 1950s and 60s. Finally, training of military medical personnel for medical operations in the nuclear environment has been woefully inadequate in recent years. The Surgeons-General have recognized this fact and have mandated the Armed Forces Radiobiological Research Institute to expand its educational program on radiation injury. In the following three articles we propose to provide the military medical officer with an overview of the current state of knowledge on the pathophysiology of radiation injury, concepts of combined injury, and infectious disease processes in the radiation or combined injury casualty.

Pathophysiology of Acute Radiation Exposure

Cellular Radiobiology

Ionizing radiation damages living tissue by chemically altering critical cellular constituents. The degree to which ionizing radiation damages tissue is a function of several factors. The amount of cellular damage is proportional to the total Radiation Absorbed Dose (RAD). However, cellular damage will also vary with the quality of radiation and the dose of exposure. Particulate ionizing radiations (neutrons, alpha particles, beta particles) are densely ionizing and deposit their energy in short path lengths.[1] These radiations have been defined as high Linear Energy Transfer (LET) radiations. The damage may be either direct through the absorption of radiation energy by the critical cellular constituents; or through the indirect action of chemically reactive free-radical species produced by ionizing radiation. Figure 1 represents the hypothesized mechanisms for direct effects of ionizing radiation on biologic materials. High LET radiations damage tissue primarily through their direct effects on critical cellular constituents. Photon radiations (x-rays and gamma-rays) are less densely ionizing and exert their biologic effect

The number of ionizations is the same in each cell.
The ionizations from neutrons are clustered, whereas those from X- or gamma rays are diffusely distributed.
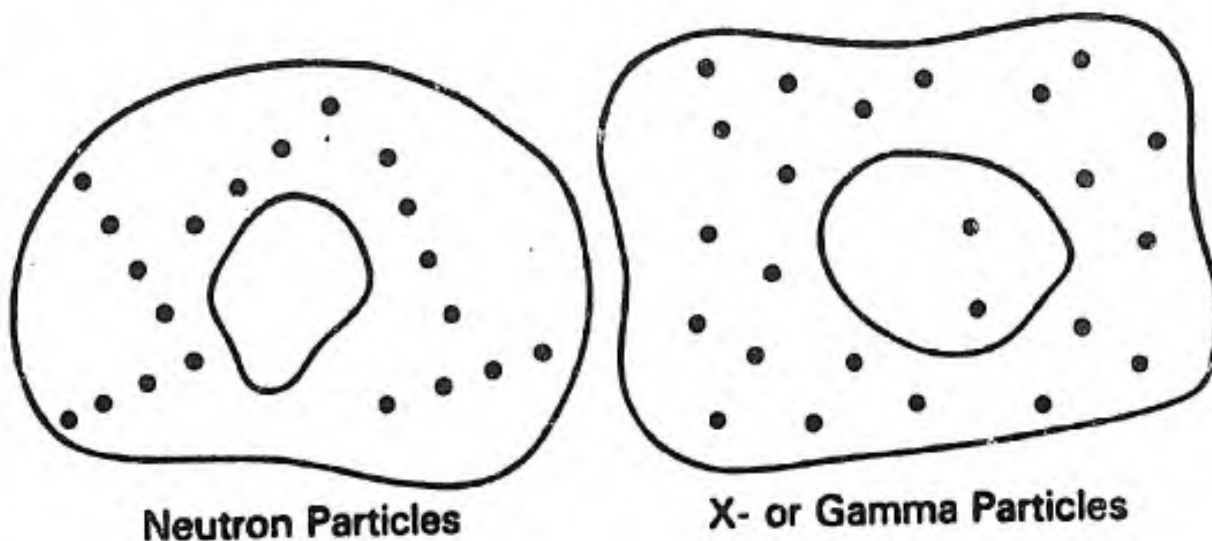

Neutron Particles   **X- or Gamma Particles**

Figure 1a. Distribution of ionization from particular radiation.
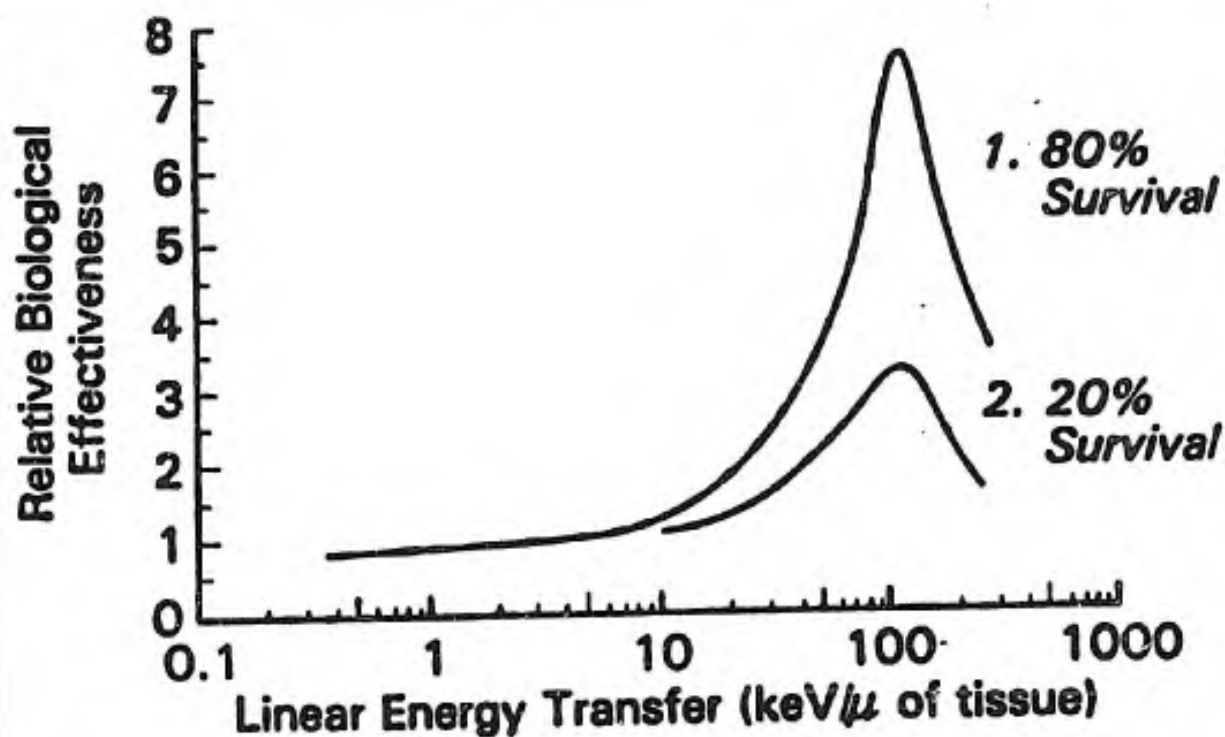

1. 80% Survival

2. 20% Survival

Figure 1b. RBE plot as a function of LET for damage to in vitro cells.

primarily via the indirect action of free-radicals. The free radicals are produced by excitation of molecules and radiolysis of cellular water producing intracellular ions. These highly reactive free radical moieties can then react with many critical macromolecules (enzymes, nucleic acids, proteins) to disrupt cellular function.[3] Cellular damage due to photon radiation can be reversed through normal cell repair mechanisms. However, if the rate of damage production exceeds the normal repair capacity, cell damage will be permanent or will result in cell death. Low LET radiations, low total dose exposures and low dose rate exposures will permit significant cellular repair. Relative biological effectiveness (RBE) increases with increasing LET, and is related to the ratio of the high LET to low LET radiation dose to produce the same biological effect.[3] Deoxyribonucleic acid (DNA) appears to be the principle cellular constituent, which, when altered by ionizing radiation, will lead to cell death. DNA is particularly sensitive to the effects of ionizing radiation when it is being replicated or transcribed. Thus rapidly proliferating or differentiating tissues are more susceptible to the damaging effects of ionizing radiation.[4]

The pathology of the acute radiation syndrome has previously been defined in relation to damage to major organ systems that result in the secondary pathology.[5] Four major organ systems are particularly sensitive to injury from radiation: hematopoietic (blood forming); gastrointestinal; microvascular or cardiovascular; and central nervous system. The degree to which each organ system is damaged is a function of radiation exposure dose. The lethal dose of irradiation from low LET radiation for 50% on humans in 60 days is approximately 286 rads midline tissue dose.[6]

Hematopoietic Syndrome

All red and white blood cells are derived from a single line of pluripotential stem cells. Upon appropriate activation, either immunologic or erythropoietic, the stem cells undergo primary differentiation into committed stem cells, followed by further differentiation into mature blood components. This involves rapid proliferation and marked radiosensitivity. The mature lymphocyte is also extremely radiosensitive, experiencing an intermitotic death.[7] Figure 2 represents the decline of the circulating levels of several blood components following whole body irradiation. The rapid fall of circulating lymphocytes during the first 48 hours following acute radiation exposure is a very characteristic response. The most rapid and reliable estimate of potentially lethal radiation exposure is made by quantitative lymphocyte counts. The less rapid fall of granulocytes, platelets, and erythrocytes is representative of failure to replace these blood components with newly differentiating cells. Figure 3 describes the relationship between radiation exposure dose and blood

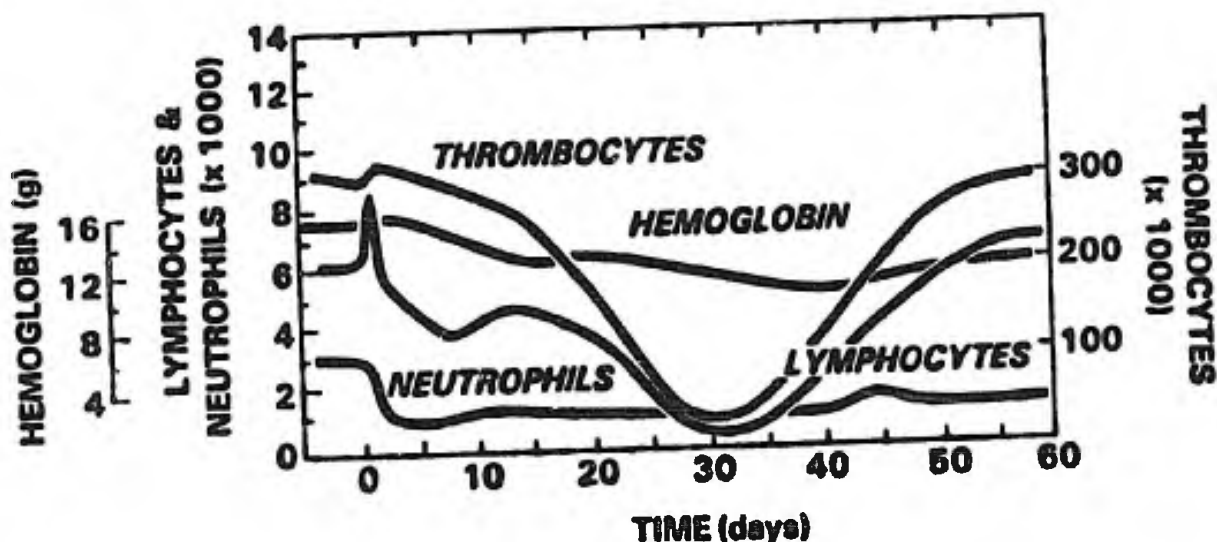# HEMATOLOGICAL RESPONSE to 300 rads
WHOLE-BODY EXPOSURE

Figure 2. Shows the changes in blood component against time compared to radiation.

cell concentrations. It should be noted that radiation exposure doses can be approximated from this relationship.

Secondary pathologies associated with the bone marrow syndrome are increased susceptibility to infection and hemorrhage due to loss of white cells and platelets. Indeed the risk of infection is the most life threatening sequela of radiations in the range of 200 to 800 rads whole body exposure. The clinical management of the irradiated casualty and the problem of opportunistic infection following irradiation will be addressed in the two subsequent manuscripts. For triage, the signs and symptoms associated with the pancytopenia are: chills, fever, oral and pharyngeal ulceration, malaise, fatigue, dyspnea, pneumonia, enteritis with diarrhea and hematochezia, and a hemorrhagic diathesis.

The latent period is a time of relative well-being that follows regression of the prodromal symptoms. The duration of this period can be days to weeks, and it is dose-dependent. The period of manifest illness results from the initial radiation insult to the organ systems at the time of exposure. Pancytopenia is the primary cause of illness at or below midlethal levels of whole-body exposure.

Gastrointestinal Syndrome

The epithelium of the small intestine is nearly as radiosensitive as the bone marrow, and it plays a significant role in determining survival after exposure to high doses of radiation. At doses of approximately 100 rads, gastrointestinal (GI) disturbances result from decreased cell production in small intestinal crypts, loss of cells covering the villi, and subsequently denuded villi.[6] In addition, epithelial cell tight junctions may be disrupted, thereby creating a portal by which bacterial endotoxins and gut microflora may gain entry to the systemic circulation.[9]

At radiation dose exposures, above approximately 800 rads

whole body exposure, there will be significant destruction of GI epithelium. GI transport epithelium is normally replaced on a 8-day cycle. Differentiating intestinal stem cells in the crypts of Lieberkuehn proliferate and differentiate as they progress up the intestinal villae. Radiation will kill the intestinal stem cells and prevent the replacement of mature transport epithelium as they are normally sloughed off from the tips of the villus. Figure 4 shows the result of acute radiation on intestinal crypts 48 hours following the exposure of crypt stem cell populations. While epithelial cells in various stages of differentiation can be seen lining the villus, there is an obvious lack of lower crypt cells. Complete destruction of the crypt stem cells will result in a total loss of GI transport capability within a week. Clinically, this loss of transport epithelium will result in severe diarrhea with consequent loss of fluid and electrolytes. Other stigmata include: severe vomiting,

RELATIONSHIP BETWEEN

EARLY CHANGES IN PERIPHERAL BLOOD LYMPHOCYTE COUNTS

AND

DEGREE OF RADIATION INJURY

NORMAL RANGE

MODERATE

SEVERE   INJURY

VERY SEVERE

LETHAL

ABSOLUTE LYMPHOCYTES

3000
2000
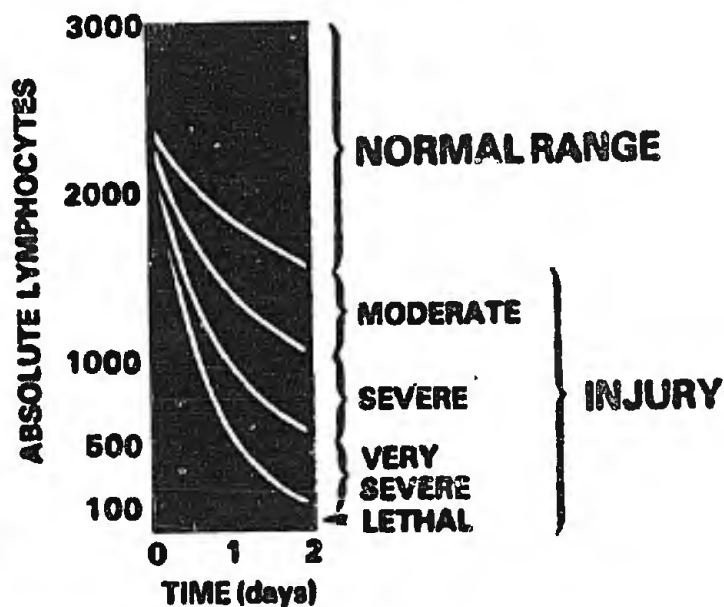1000
500
100

0   1   2

TIME (days)

Figure 3. Shows the relationship between the decrease in early lymphocyte counts as a function of radiation exposure.
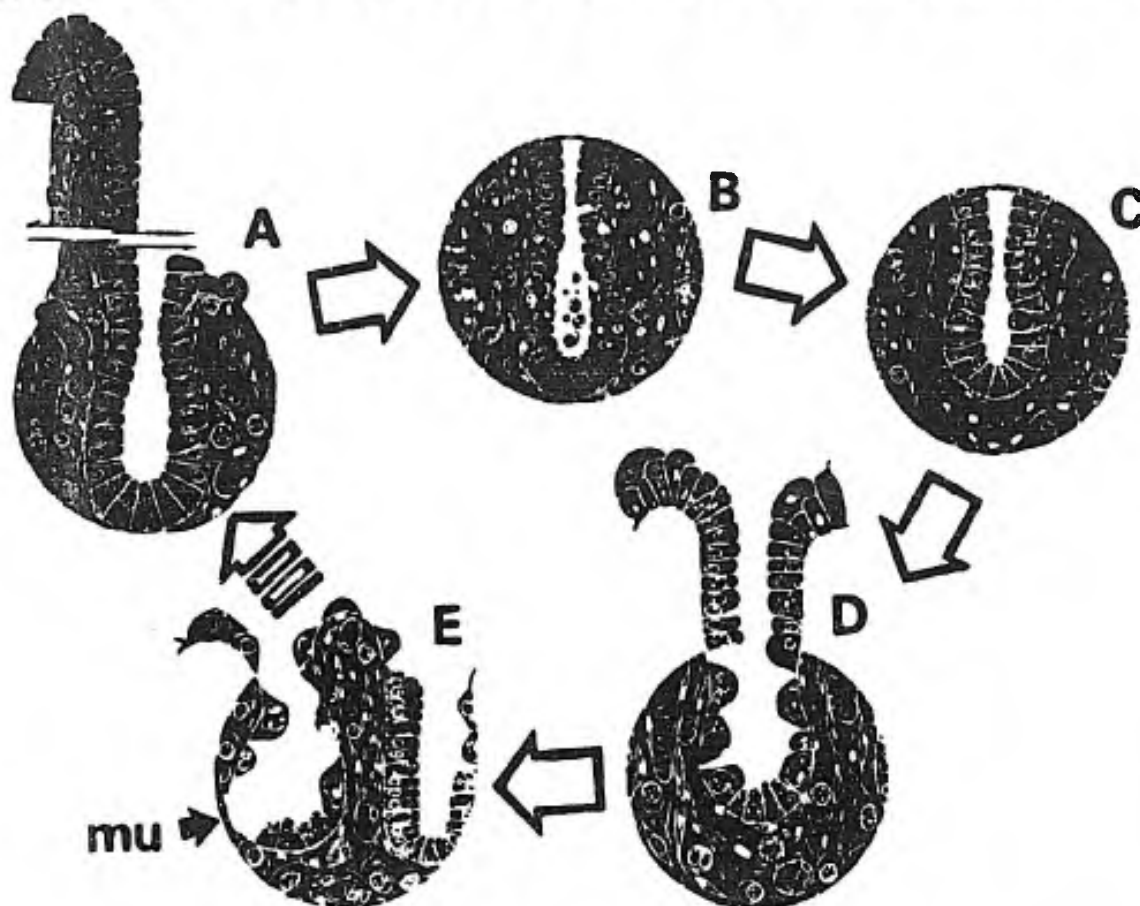
RADIATION-INDUCED CRYPT DAMAGE

Figure 4. Shows the changes in the intestinal crypt cells as they are sloughed from the small bowel after radiation.

hemorrhagic diarrhea, malabsorbtion, paralytic ileus, renal insufficiency. Acute shock secondary to the extreme fluid loss will present the most life-threatening challenge.

Microvascular and Central Nervous System

Radiation exposures in excess of those causing the gastrointestinal syndrome will cause increases in vascular permeability.[10] This results in a tremendous extravasation of intravascular fluids and an inability to maintain blood pressure and tissue perfusion despite volume replacement and the use of pressor drugs. Severe nausea, vomiting, and explosive diarrhea occurs with-

in minutes to several hours after irradiation. Malaise, weakness, ataxia and seizures may also occur. Death will ensue within hours to several days from subsequent intractable shock.

Triage

The dose associated with the various facets of the Acute Radiation Syndrome is not useful in triage for several reasons. The radiation exposure levels only apply to photon irradiations. Prompt irradiation from tactical nuclear weapons which may be employed in the European Theater will generally average three neutron rads to each photon rad. As mentioned earlier

the effects of particulate irradiation may greatly exceed that of photons. The effect may only be 50% greater in the hematopoietic system but may be two to four times as great in the gastrointestinal system. The response of any given individual may vary greatly and a nonhomogenous exposure of radiation (especially if bone marrow and gut are spared) may result in a markedly decreased effect. Additionally, United States forces do not carry personal dosimeters that measure neutron and photon exposure. Finally, dose rate effects can be very profound. This is particularly true in a fallout environment. In this situation, tactical

dosimeters (two per platoon) may be useful to a commander deciding whether to commit exposed troops to battle, but less useful to the health care provider. Other problems will also be extant. Casualties will be numerous and resources certainly will be inadequate. Complicating this will be the addition of blast and thermal injuries. The issues of combined injuries will·be addressed in more detail in parts II and III of this paper. The goal of all medical personnel should be to allocate precious resources to salvage the maximum number of casualties.

The following guidelines apply to medical personnel operating in austere field conditions and are based on recent recommendations.[11] In situations where medical resources are available (accidents, terrorists) many of the concepts discussed in parts II and III may apply. In particular, the use of lymphocyte levels may be used as a biologic dosimeter (estimate of radiation injury). It is vital to remember that there is no immediate life threatening hazard for an irradiated person with exposures that are survivable. Therefore, treatment must be directed toward primary resuscitation for other injuries (burns, penetrating wounds, blast). Additionally, if it is known that chemical or biological agents have not been used, resuscitation should precede decontamination as there is no hazard to medical personnel treating the patient.

Due to difficulty in establishing an early definitive diagnosis, it is best to function within a simplified, tentative classification system based on three possible categories of patients (Table I):

I. Radiation Injury Unlikely

If there is an absence of any symptoms associated with significant radiation injury, patients are judged to be at minimal risk for radiation complications. These patients should be triaged according to the severity of conventional injuries. If

Table I. Preliminary Triage of Casualties with Possible Radiation Injuries.

Symptoms	Radiation Injury		
	Unlikely	Probable	Severe
Nausea	–	+ +	+ + +
Vomiting	–	+	+ + +
Diarrhea	–	±	± to + + +
Hyperthermia	–	±	+ to + + +
Hypotension	–	–	+ to + +
Erythema	–	–	– to + +
CNS Dysfunction	–	–	– to + +

the patients are free of conventional injuries or disease states that require treatment, they should be released and returned to duty.

II. Radiation Injury Probable

Anorexia, nausea, and vomiting will be the primary prodromal symptoms associated with radiation injury. Priority for further evaluation will be assigned after all life-threatening injuries have been stabilized. Casualties in this category will not require any medical treatment within the first few days for their radiation injuries. Evidence to support the diagnosis of significant radiation injury may be obtained from lymphocyte assays taken over the next two days. If the evidence indicates that a significant radiation injury was received, these casualties need to be monitored for pancytopenic complications.

III. Radiation Injury Severe

These casualties are judged to have received a radiation dose that is potentially fatal. Nausea and vomiting will be almost universal for a person in this group. In addition, the prodromal phase may include prompt explosive diarrhea, significant hypotension, and signs of neurologic injury. These patients should be sorted according to the availability of resources. Patients should receive symptomatic care. Lymphocyte analysis is necessary to support this classification.

Symptoms Frequently Occurring in Whole-Body Irradiated Casualties Within First Few Hours Post-Exposure

Nausea and Vomiting

These symptoms occur with increasing frequency as the radiation exceeds 100 to 200 rads. Onset may be as long as six to twelve hours postexposure, but symptoms usually subside within the first day. Occurrence of vomiting within the first hour, especially if accompanied by explosive diarrhea, is associated with doses that frequently prove fatal. Due to the transient nature of these symptoms, it is possible that the patient will have already passed through this initial phase of gastrointestinal distress before being seen by a physician. It will be necessary to inquire about these symptoms at the initial examination. Emotional stress may also precipitate a similar gastrointestinal response and will certainly complicate the diagnosis.

Hyperthermia

Casualties who have received a potentially lethal radiation injury show a significant rise in body temperature within the first few hours postexposure.[5] Although the number of cases is few, this appears to be a consistent finding. Occurrence of fever and chills within the first day postexposure is associated with a severe and life-threatening radiation dose. Hyperthermia may occur in patients who receive lower but still serious radiation doses. (200 rads or more). Present evidence indicates that hyperthermia is frequently overlooked.

Erythema

A person who received a whole-body radiation dose of more than 1000 to 2000 rads will experience erythema within the first day postexposure. This is also true for those who received comparable doses to a local body region, where the erythema is restricted to the affected area. With doses lower but still in

the potentially fatal range (200 rads or more), erythema is less frequently seen.

Hypotension

A noticeable and sometimes clinically significant decline in systemic blood pressure has been recorded in victims receiving a supralethal whole-body radiation dose.[10] A severe hypotensive episode was recorded in one person who had received several thousand rads. In persons receiving several hundred rads, a systemic blood pressure drop of above 10% has been noted. Severe hypotension after irradiation is associated with a poor prognosis.

Neurologic Dysfunction

Experience indicates that almost all persons who demonstrate obvious signs of damage to the central nervous system within the first hour postexposure have received a supralethal dose.[10] Symptoms include mental confusion, convulsion, and coma. Intractable hypotension will probably accompany these symptoms. Despite vascular support, patients succumb within 48 hours.

If the physician has the resources of a clinical laboratory, additional information can be obtained to support the original working diagnosis suspected by the presence of prodromal symptoms. An initial blood sample for concentration of circulating lymphocytes should be obtained as soon as possible from any patient classified as "Radiation Injury Possible" and "Radiation Injury Probable." At the completion of the initial assessment, or at least no later than 24 hours after the event in question, additional comparative blood samples should be taken:

(1) Lymphocyte levels in excess of 1500/mm³: Minimal likelihood of significant dose that would require treatment.

(2) Lymphocyte levels between 1000 and 1500/mm³: May require treatment for moderate depression in granulocytes and platelets within three weeks postexposure.

(3) Lymphocyte levels between 500 and 1000/mm³: Will require treatment for severe radiation injury and should be hospitalized to minimize the complications from hemorrhage and infection that will arise within two to three weeks postexposure.

(4) Lymphocyte levels of less than 500/mm³: Have received a radiation dose that may prove fatal. All patients need to be hospitalized for the inevitable pancytopenic complications.

(5) Lymphocytes are not detectable: Have received a supralethal radiation dose and survival is very unlikely. Most patients have received severe injuries to their gastrointestinal and cardiovascular systems and will not survive for more than two weeks.

Since the previous guidelines will not be available in austere conditions, a useful rule of thumb would be: If lymphocytes have decreased by 50% and are less than 1000/mm³, the patient has received a significant radiation exposure. In the event of combined injuries the use of lymphocytes may be unreliable. Patients who have received severe burns or multi-system trauma often develop lymphopenia.

Casualties who have received a potentially fatal dose of radiation will most likely experience a pattern of prodromal symptoms that are associated with the radiation exposure itself. Unfortunately, these are nonspecific and may be seen with other forms of illness or injury, which may complicate the process of diagnosis. Therefore, the triage officer must determine the symptoms that have occurred within the first day postexposure, evaluate the possibility that they are indeed related to radiation exposure, and then assign the patient to one of the three categories: "Radiation Injury Unlikely,"

"Radiation Injury Probable," "Radiation Injury Severe." In the last two categories, the study of changes in circulating lymphocytes may support or rule out the original working diagnosis. All combined-injury patients should be treated initially as if no significant radiation injury is present. Triage and care for any life-threatening injuries should be rendered without regard to the probability of radiation injury. The physician should make a preliminary diagnosis of radiation injury only for those patients for whom radiation is the sole source of the problem. This is based on the appearance of nausea, vomiting, diarrhea, hyperthermia, hypotension, and neurologic dysfunction.

Initial Treatment for Patients with Whole-Body Radiation Injury

For those casualties who have received sublethal whole-body radiation doses, gastrointestinal distress will predominate in the first two days. Antiemetics may be effective in reducing symptoms. Unless severe radiation injury has occurred, these symptoms will usually subside within the first day. For those patients who continue to experience gastrointestinal distress, parenteral fluids should be considered. If explosive diarrhea occurred within the first hour postexposure, fluids and electrolytes should be administered if available. For triage purposes, the presence of explosive diarrhea (especially bloody) is likely to be related to a fatal radiation dose. Cardiovascular support for patients with clinically significant hypotension and neurologic dysfunction should be undertaken only when resources and staff allow. These patients are not likely to survive injury to the vascular and gastrointestinal linings combined with marrow aplasia.

Diagnosis and Treatment of the Patient with Combined Injuries

In the event of a radiation accident or nuclear detonation, many patients

will probably suffer additional injuries. Initial triage of patients is based on the existence of the conventional injuries. Further reclassification may be warranted on the basis of prodromal symptoms associated with radiation injury. Animal studies indicate that infections are much more difficult to control and wounds and fractures heal more slowly when accompanied by sublethal doses of radiation. Potentially, survivable burns and trauma will be fatal in a large percentage of persons who have received significant injury from sublethal radiation. Patients requiring surgical intervention should have the procedures performed as soon as possible (within 36 hours), due to the risk of complications arising from pancytopenia. Patients with severe radiation injury, are classified "expectant" despite "potentially survivable" conventional injuries. These issues are addressed in part II and III in much greater detail.

The Contaminated Patient

Radiation injury per se does not imply that the patient is a health hazard to the medical staff. Studies indicate that the levels of intrinsic radiation, present within the patient (after exposure to neutron and photon sources), are not life-threatening hazards.

Patients entering a medical treatment facility should be routinely decontaminated if monitoring of radiation is not available. Removal of the patient's clothing will usually reduce most of the contamination. Washing exposed body surface will further reduce this problem. Both of these procedures can be performed in the field or on the way to the treatment facility. Once the patient has entered the treatment facility, care should be based on the obvious injuries. Care for life-threatening injuries should not be delayed until decontamination procedures are completed.

When radiation safety personnel are available, decontamination procedures will be established to assist in rendering care and to minimize the hazard from radioactive contaminants. A more extensive decontamination procedure is to scrub the areas of persistent contamination with a mild detergent or diluted solution. Caution should be taken not to disrupt the integrity of the skin while scrubbing, which could lead to incorporation of the radioisotopes into deeper layers of the skin. Contaminated wounds should be addressed first, since they will rapidly incorporate the contaminant. Washing, gently scrubbing, or even debridement may be necessary to reduce the contaminant level.

Wearing surgical attire will reduce the possible contamination of health personnel. If additional precautions are warranted, rotation of the attending personnel will further reduce the possibility of significant contamination or exposure. Inhalation or ingestion of radioactive particles is a much more difficult problem and resources will not be available in a field situation. Therefore, prevention of incorporation is paramount.

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